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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

HADDAD, MAHER M

ART UNIT

PAPER NUMBER

1644

DATE MAILED: 09/24/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/734,628

Applicant(s)

CHINNAIYAN ET AL.

Examiner

Maher M. Haddad

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 76-98 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 76-98 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

1. Claims 76-98 are pending and under consideration.
2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/30/03 has been entered.
3. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
4. Claims 87-91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
 - A. The recitation "illumination domain comprises a luciferin protein" in claim 87, lines 5-6 is ambiguous and indefinite. It is unclear how would the illumination domain comprises a luciferin reagent and the imaging agent is also luciferin. It is unclear how can the light-generating moiety and its substrate are the same.
5. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
6. Claims 76-98 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrases "imaging agent" and "wherein said cells possess or are suspected of possessing polypeptides comprising RGD motifs" claimed in claims 76, 80, 87 and 92, lines 1-3, the phrase "ex vivo" claimed in claims 77, 81, 88, and 93, lines 1-2 and the phrase "cells comprise tumor cells" claimed in claim 78, 85, 89 and 94 represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 6/30/03 does not point to the specification for support for the newly added limitations "imaging agent" and "wherein said cells possess or are suspected of possessing

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polypeptides comprising RGD motifs” as claimed in claims 76, 80, 87 and 92, “*ex vivo*” as claimed in claims 77, 81, 88, and 93 and “cells comprise tumor cells” claimed in claim 78, 85, 89 and 94. However, the specification does not provide a clear support of these limitations. The instant claims now recite limitations which were not clearly disclosed in the specification and claims as originally filed.

7. Claims 76-98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for *in situ* or *in vivo* imaging of a tumor neovasculature in an individual comprising administration a chimeric polypeptide wherein the chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1 does not reasonably provide enablement for a method of imaging, comprising: providing any cells, a chimeric polypeptide and a imaging agent in claim 76; a method of imaging, comprising providing any cells, a chimeric polypeptide and any imaging agent in claim 80, a method of imaging, comprising providing any cells, any chimeric polypeptide and an imaging agent wherein said chimeric polypeptide comprises any illumination domain, and any target recognition domain, wherein said illumination domain comprises a luciferin protein, wherein said target recognition domain comprises any RGD sequence, wherein said imaging agent is luciferin in claim 87; a method of imaging comprising providing any cells, any chimeric polypeptide, any imaging agent, wherein said chimeric polypeptide comprises an illumination domain, and any target recognition domain, wherein said illumination domain comprises a bioluminescent polypeptide, wherein target recognition domain comprises any “RGD sequence”, wherein said cells comprise ex vivo cells in claims 77, 81, 88, and 93, wherein cells comprise tumor cells in claims 78, 85, 89 and 94. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification disclosure does not enable one skilled in the art to practice the invention without any undue amount of experimentation.

Besides a chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1 for *in vitro in situ* or *in vivo* imaging of a tumor neovasculature, the specification fails to provide any guidance as to how to make and how to use any “chimeric molecule” for *in vitro in situ* or *in vivo* imaging of any cell, comprising providing any imaging agent.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples,

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the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Applicant has not provided sufficient biochemical information that distinctly identifies such “any cells” possess or are suspected of possessing polypeptides comprising RGD motifs, “chimeric molecule” comprises a luciferin protein or any RGD sequence other than the chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1. While any “RGD motifs” may have some notion of “integrin recognition”, claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents, commensurate in scope with the claimed invention. The specification (page 15, lines 10-25) fails to provide any guidance on how to make RGD motif-comprising polypeptide, any chimeric molecule, any pharmaceutical formulation, any imaging device can be used for *in situ* or *in vivo* imaging a tumor neovasculature in an individual. Further, beside luciferin, the specification fails to disclose any imaging agent that would act as a substrate for any chimeric protein.

The term “comprises” in claims 87 and 92 is open-ended, it expand the “RGD sequence” to include additional non disclosed amino acids the N-, C- or both termini of the “RGD sequence”. There is insufficient guidance as to which amino acid segments within the polypeptide can be unique and retain a distinct functional capability of “RGD motif-comprising polypeptide”. Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein’s structure will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural property, predictability of which amino acid fragment can retain the functional capabilities of the RGD motif-comprising polypeptide requires knowledge of, and guidance with regard to, which segments in the polypeptide’s sequence contribute to its function.

Minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Therefore, structurally unrelated compounds comprising any “RGD sequence” would be expected to have greater differences in their activities. Further, RGD sequence is the primary site of recognition by integrins that are expressed on tumor cells and are responsible for tumor invasion. Therefore, there is insufficient direction and guidance as to how the method for *in vitro*, *in situ* or *in vivo* imaging of any cell will be accomplished with the RGD-motif-comprising polypeptide.

Therefore, there is insufficient direction or objective evidence as to how to make and to how to use any chimeric molecule comprising RGD motif-comprising polypeptide which can be used for *in situ* or *in vivo* imaging of tumor neovasculature for the number of possibilities associated with the myriad of direct and indirect effects associated with various “chimeric

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molecule” and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. Claims 76-98 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method for *in situ* or *in vivo* imaging of a tumor neovasculature in an individual comprising administration a chimeric polypeptide wherein the chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:.

Applicant is not in possession of a method of imaging, comprising : providing any cells, a chimeric polypeptide and a imaging agent in claim 76; a method of imaging, comprising providing any cells, a chimeric polypeptide and any imaging agent in claim 80, a method of imaging, comprising providing any cells, any chimeric polypeptide and an imaging agent wherein said chimeric polypeptide comprises any illumination domain, and any target recognition domain, wherein said illumination domain comprises a luciferin protein, wherein said target recognition domain comprises any RGD sequence, wherein said imaging agent is luciferin in claim 87; a method of imaging comprising providing any cells, any chimeric polypeptide, any imaging agent, wherein said chimeric polypeptide comprises an illumination domain, and any target recognition domain, wherein said illumination domain comprises a bioluminescent polypeptide, wherein target recognition domain comprises any “RGD sequence”, wherein said cells comprise ex vivo cells in claims 77, 81, 88, and 93, wherein cells comprise tumor cells in claims 78, 85, 89 and 94.

Applicant has disclosed only a chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1, luciferin as the substrate and the tumor cell line MDA-435 and the orthotopic mammary tumor in a nude mouse; therefore, the skilled artisan cannot envision all the contemplated chimeric molecule, cells, and image agent possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1 “Written Description” Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying

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characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.) Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant's arguments, filed 6/30/03 (Paper No. 19), have been fully considered, but have not been found convincing.

Applicant draws the Examiner's attention to example 1 of the specification which provides a distinct use of the present invention.

While example 1 is drawn to a molecular imaging approach to non-invasively detect neovascularization within tumors in vitro and in vivo, using an RGD-containing-luciferase fusion protein and luciferin (page 26). The example does not satisfy the requirement of 112, first paragraph under both enablement and written description because the example does not provide a method of imaging of any cell neither does it provide any RGD sequence or any imaging agent.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

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10. Claims 76-98 are rejected under 35 U.S.C. 103(a) as being obvious over U.S Patent No. 5,650,135 (IDS reference AB), in view of U.S Patent No. 6,087,476 (IDS reference AA) and U.S Patent No. 6,180,084 (of record).

The '135 patent teaches methods and compositions relating to non-invasive imaging and/or detecting of light-emitting conjugates in mammalian subjects (*in vivo*). The conjugates contain a biocompatible entity and a light-generating moiety. Biocompatible entities include, but are not limited to, small molecules; macromolecules; microorganisms; eukaryotic cells; all types of pathogens and pathogenic substances; and particles (column 7, lines 13-21 in particular). Light-generating moieties are typically molecules or macromolecules that give off light. They may generate light as a result of radiation absorption (e.g. fluorescent or phosphorescent molecules), or as a result of a chemical reaction (e.g. bioluminescent proteins). Exemplary light-generating moieties are bioluminescent proteins, such as luciferase and aequorin (column 2 lines 63-67 and column 3 lines 1-5 in particular). Luciferases require a substrate, such as luciferin (column 10, lines 33-35 in particular). The method includes administering to the subject a conjugate of the entity and a light-generating moiety (column 2, lines 63-64 in particular).

The claimed invention differs from the reference teachings only by the recitation that the chimeric molecule comprising a first domain comprising a bioluminescent and a second domain comprising an RGD motif-comprising polypeptide.

The '084 patent teaches a tumor homing molecule is linked to a moiety that is detectable external to the subject, thereby providing a composition useful to perform an *in vivo* diagnostic imaging study. For example, *in vivo* imaging using a detectable labeled tumor homing peptide can identify the presence of a tumor in a subject (column 37, lines 4-9 in particular). A tumor homing molecule binds specifically to a sample of the tumor obtained from the patient. For example, the RGD-4C (CDCRGDCFC; claimed and reference SEQ ID NO:1) binds to blood vessels in microscopic sections of human tumors, whereas little or no binding occurs in the blood vessels of non-tumor tissues (column 25, lines 46-52 in particular). Furthermore, tumor homing molecules can bind to the endothelial lining of small blood vessels of tumors. The vasculature within tumors is distinct, presumably due to the continual neovascularization, resulting in the formation of new blood vessels required for tumor growth. The distinct properties of the angiogenic neovasculature within tumors are reflected in the presence of specific markers in endothelial cells and pericytes (column 35, lines 44-50 in particular).

The '476 patent teaches chimeric proteins obtained by genetic engineering. Such chimeric proteins comprise a continuous polypeptide sequence in which a photoprotein is linked to an antigenically active protein or fraction thereof. The '476 patent further teaches that chimeric proteins which comprise a continuous polypeptide sequence in which a photoprotein is linked to a protein with specific affinities for analytes of interest and methods of using these proteins in immunodiagnostic or imaging processes (column 1, lines 15-28 in particular). The chimeric protein constructed as a continuous polypeptide sequence and comprised of a photoprotein and a second protein. The photoprotein is a protein having luminescent properties and is typically chosen from a class of compounds known as luciferases. Finally, the '476 patent teaches that the

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chimeric proteins can be used to detect antibodies, antigens, or other specifically binding proteins. The '476 patent further teaches that a chimeric protein possessing specific affinity for analytes of as a chimeric protein possessing epitopes of an analyte (either immunoglobulins or antigens or portions thereof, and incorporating a photoprotein, would be of great value in immunoassay systems (see col., 1, lines 44-50 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to link the RGD containing peptide (claimed SEQ ID NO:1) taught by '084 patent with the photoprotein with luminescent properties and such chimeric proteins would be of great value in immunoassay systems taught by the '476 patent and use the resultant chimeric molecule in the methods of imaging taught by the '135 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the tumor homing RGD-containing peptide binds specifically to a sample of the tumor obtained from the patient taught by '476 patent and the resultant chimeric protein can be used to detect specific binding proteins taught by '476 which reflect in the presence of specific markers in endothelial cells taught by the '084 patent wherein such imaging method is a non-invasive and allows the detecting of light-emitting conjugates in mammalian subjects as taught by the '135 patent

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 6/30/03 (Paper No. 19), have been fully considered, but have not been found convincing.

Applicant asserts that the newly submitted claims are non-obvious. Applicant argues that findings of motivation to combine prior art must be based on objective evidence of record, and not on hindsight reconstruction. Applicant argues in conjunction with case laws that an Examiner must make a showing of the teaching or motivation to combine prior art references. Applicant further argues that the Examiner relies upon *In re McLaughlin*, as establishing that "there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art". Applicant argues that the extent that this 1969 and 1971 cases appear to condone hindsight reconstruction when providing a motivation to combine references, the Federal Circuit has overruled this proposition and has emphatically stated that hindsight reconstruction is not proper. Applicant argues in conjunction with case law that the Federal Circuit has warned against using hindsight reconstruction as a test of obviousness.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a

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sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971). See MPEP 2145.

The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See MPEP 2144.

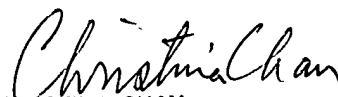
In the instant case, given the teachings of '476 patent that the tumor homing RGD-containing peptide binds specifically to a sample of the tumor obtained from the patient and the resultant chimeric protein can be used to detect specific binding proteins which reflect in the presence of specific markers in endothelial cells as taught by the '084 patent wherein such imaging method is a non-invasive and allows the detecting of light-emitting conjugates in mammalian subjects as taught by the '135 patent. One of ordinary skill in the art at the time the invention was made would have been motivated to link the RGD containing peptide (claimed SEQ ID NO:1) taught by '084 patent with the photoprotein with luminescent properties and such chimeric proteins would be of great value in immunoassay systems taught by the '476 patent and use the resultant chimeric molecule in the methods of imaging taught by the '135 patent.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
September 22, 2003


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